REMARKS

I. Status of Claims

Currently, claims 1-10, 12-18, 21-29, and 40-52 are pending in this application. Claims 1-10, 13, 15, 25-29, and 40-46 stand rejected.

Applicant has canceled non-elected claims 31-39 without prejudice or disclaimer and reserves the right to pursue the canceled subject matter in one or more divisional applications. Claims 12, 14, 16-18, and 21-24 have been withdrawn from consideration by the Office as directed to non-elected inventions.

Applicant has added claims 47-52. Support for claims 47-48 can be found throughout the specification, including, for example, at page 48, lines 22-24. Support for claims 49-50 can be found throughout the specification, including, for example, at page 11, lines 13-16. Support for claims 51-52 can be found throughout the specification, including, for example, at page 26, lines 12-16. Accordingly, no new matter is added.

II. Rejections Under 35 U.S.C. §112, First Paragraph

1. Claims 1-10, 13, 15, 25-29, and 40 Are Enabled

The Office maintains the rejection of claims 1-10, 13, 15, 25-29, and 40 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Office Action at page 4. The Office acknowledges that the specification enables the claimed subject matter for a

range of pH from 9.3 to 10, but asserts that it "does not reasonably provide enablement for a range of pH 9.3 to 14." *Id.* Applicant respectfully traverses this rejection.

An Applicant's specification is ***presumptively enabled*** for the full scope of the claims. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971) (emphasis added); *accord*, M.P.E.P. § 2164.04. In fact, "[a]s a matter of Patent Office practice . . . [a specification] must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements." *In re Armbruster*, 185 USPQ 152, 153 (C.C.P.A. 1975).

The M.P.E.P. specifically states that the Office has the initial burden to establish a reasonable basis to question the enablement of the claimed invention. M.P.E.P. § 2164.04. This reasonable basis may be established by the Office by "making specific findings of fact, supported by evidence, and then drawing conclusions based on these findings of fact". . . "[h]owever, specific technical reasons are always required." *Id.* Absent such evidence, the burden does not shift to the Applicant. *In re Marzocchi*, 169 USPQ at 369.

Here, the specification discloses that the fusion DNA polymerases and fusion DNA polymerase blends of the invention will work at a high pH (*i.e.*, 9.1 to 14). Specification at page 26, lines 17-23; see also, page 12, lines 17-20. The working examples in the specification also show that Applicant's fusion DNA polymerases operate efficiently at the high pH ranges tested, including, between pH 9.5 and 12. The Office provides no *reasonable* basis to doubt the objective truth of the statements in the specification.

Instead, the Office relies on U.S. Patent No. 4,545,933 to Ernster ("the '933 patent") Ernster and its teaching about preparing hydrolyzed protein from *casein* as evidence that the fusion DNA polymerases and fusion DNA polymerase blends of the invention will not work over the full range of pH 9.3 to 14, and in particular, pH 12 to 14. Specifically, the Office asserts that

> the hydrolysis of protein at pH 10 and higher, as taught by Ernster (1985) more than meets this initial burden. Furthermore, as known by one of ordinary skill in the art and conveyed by Ernster (see column 6 lines 19-23) as the pH increases, protein hydrolysis increases. Thus *a working example of a protein at pH 10.0* provides no evidence of that protein working at higher pH, especially in the range of pH 12-14 where Applicant has no working examples.

Office Action at page 4 (emphasis added).

While the Office points to a working example at pH 10, the specification, in fact, discloses working examples up to pH 12. (*See e.g.*, Figure 2, showing strong bands of amplified product at pH 12 for a blend and Figure 6 showing strong bands of amplified product at pH 11.8 for a DNA polymerase fusion that is not part of a blend). The strong amplification bands obtained at pH 11.8 and 12 suggest that the Pfu-Sso7d fusions and polymerase blends comprising the same will similarly work at pH greater than 12. Thus, the Office overlooks the working examples showing that Applicant's Pfu-Sso7d fusions and polymerase blends comprising the same efficiently amplify DNA in reaction buffers with a pH of at least 11.8 and 12.

Furthermore, the specific teaching about the hydrolysis of casein proteins at pH 10 in the '933 patent clearly does not extend to the DNA polymerase fusions recited in the pending claims. If it did, Applicant would not have been able to demonstrate by way of working examples that

Pfu-Sso7d fusions and polymerase blends comprising the same efficiently amplify DNA in reaction buffers with a pH of 11.8 and 12. Thus, the specific teaching of the '933 patent about hydrolyzing the casein protein at pH 10 does not have general applicability to all proteins, and in particular to the DNA polymerase fusion proteins recited in the claims, as evidenced by Applicant's working examples. Accordingly, given the working examples in the specification, the '933 patent does not satisfy the Office's initial burden to establish a *reasonable* basis to question the enablement for the claimed pH range of 9.3 to 14. M.P.E.P. § 2164.04. Therefore, Applicant respectfully requests that the Office reconsider and withdraw this enablement rejection of claims 1-10, 13, 15, 25-29, and 40.

2. The Claimed Methods Do Not Omit Essential Elements

The Office rejects claims 1-10, 13, 15, 25-29, and 40-46 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Office Action at page 8. Specifically, the Office argues that the "claimed methods omit the essential element of the disclosed invention which is a blend of both a chimeric DNA polymerase fusion and a non-chimeric polymerase." *Id.* Accordingly, the Office asserts that "[t]he specification provides no support for use of one DNA polymerase fusion at pH 9.3 to 14 as claimed." *Id.* Applicant respectfully traverses this rejection.

The entire specification, including the original claims, is directed to "a DNA polymerase fusion" and methods of using the same at high pH. *See e.g.*, Specification at pages 3-8; original claims 1-39. As explained in the specification, *in one embodiment*, the DNA polymerase fusion

can be combined with another DNA polymerase to form a blend. Specifically, the specification states:

> In one embodiment, the invention provides for blends of two or more DNA polymerases comprising one or more DNA polymerase fusions of the invention with or without an additive as described herein.
>
> In a preferred embodiment, the invention provides for blends of two or more DNA polymerases comprising one or more DNA polymerase fusions and one or more mutant DNA polymerases, at least one of which is derived from *Pfu* DNA polymerase.

Specification at page 48. Thus, in certain embodiments, a DNA polymerase fusion may be combined with one or more polymerases to form a blend. However, as an "embodiment" of the invention, it is clear that a "blend" is not an essential element of Applicant's invention.

This is further born out in the examples of the specification. Example 3 describes amplification reactions at pH 10 and 11.8 using both 1) a Pfu-Sso7d DNA polymerase fusion and 2) a blend comprising a Pfu-Sso7d DNA polymerase fusion and Pfu DNA polymerase. Specification at page 78, lines 10-16; page 81, lines 3-14; and Figure 4. In amplifying a 19kb human beta globin genomic target, the Pfu-Sso7d DNA polymerase fusion alone (i.e., not as part of a blend) outperformed the blend comprising both the Pfu-Sso7d DNA polymerase fusion and a non-chimeric Pfu DNA polymerase. As noted in the specification, "[t]he reactions which have 0.83U and 1.3U Pfu-Sso7d without any cloned Pfu DNA polymerase (#3 and #4 figure 4) generated dramatically higher yields than the blend reactions (#1 and #2 figure 4) which only had 0.25U Pfu-Sso7d even though the total units of DNA polymerase were higher for the blend

reactions (2.75U #1, 5.25U #2 for the blends and 0.83U #3 and 1.3U #4 for the Pfu-Sso7d reactions - figure 4)." Specification at page 81, lines 10-14.

Accordingly, the specification provides ample support for a DNA polymerase fusion and methods of using the same as claimed. There is no requirement that the DNA polymerase fusions be part of a blend. Of course, in certain embodiments, the DNA polymerase fusions can be used in a blend with a second DNA polymerase (see e.g., specification at page 48 and new claim 47), but this is certainly not an essential element of the claimed invention. For at least these reasons, Applicant respectfully requests that the Office withdraw this rejection.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

The Office rejects claims 1-10, 13, 15, 25-29, and 40-46 under § 112, second paragraph as allegedly failing to set forth what Applicant regards as the invention. Office Action at page 9. As with the written description rejection, this rejection is based on the alleged omission of an essential element (blend of polymerases) from the claimed invention. Applicant respectfully traverses this rejection.

As discussed above in response to the written description rejection, the specification provides clear support for "a DNA polymerase fusion" as recited in the current claims without requiring that the DNA polymerase fusion be part of a blend of polymerases. In support of this 35 U.S.C. § 112, second paragraph rejection, the Office points to the Rule 132 Declaration filed with the response dated 17 December 2007 as evidence that polymerase blends are an essential

element of the invention. Office Action at page 9. Specifically, the Office asserts that in the declaration

> Applicant has stated that the Applicant was surprised to discover that increasing the pH above 9 enhances, rather than impairs, PCR efficiency of DNA polymerase fusions (plural) and blends comprising the same (see p. 5 item 18). This statement indicates that the invention is different from what is defined in the claim(s) because the claims are methods reciting one polymerase, a single DNA polymerase fusion comprising wild type *Pyrococcus furiosus* polymerase I fused to *Sulfolobus solfataricus* SSso7d protein.

Office Action at page 9.

Using the plural form of DNA polymerase fusion in the sentence noted by the Office does not indicate or even suggest that the invention is limited to blends comprising more than one DNA polymerase. Specifically, the Declaration states that "it was surprising when I discovered that increasing the pH of the reaction buffer above 9 enhances, rather than impairs, the PCR performance efficiency of the DNA polymerase fusions in U.S. Application No. 10/805,650, and blends comprising the same." Rule 132 Declaration at page 5, ¶18. As used in this sentence, "the DNA polymerase fusions in U.S. Application No. 10/805,650" simply means that the application discloses more than one DNA polymerase fusion that can be used in the methods described therein, either as the sole polymerase or as part of a blend. Using the plural form of DNA polymerase fusion does not indicate that the invention must be a blend, particularly where it is being used in a sentence that distinguishes DNA polymerase fusions from the very blends that the Office asserts are an essential element of the invention. Thus, in the context of both the Declaration itself and in the broader context of the application, which provides ample

support for using a DNA polymerase fusion, either alone or as part of a blend, the Office's position that the disclosed invention is limited to polymerase blends is without merit. Applicant respectfully requests the Office to withdraw this rejection under 35 U.S.C. § 112, second paragraph.

IV. Rejections Under 35 U.S.C. § 103

A. *Wang* Does Not Render Claims 1-4, 7-11, 13, 15, 19, 25-30, and 41-46 Obvious

The Office maintains the rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 under 35 U.S.C. § 103(a) as allegedly obvious over WO 01/082501 (*Wang*). Office Action at page 5. The Office also rejects new claims 41-46 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang*. *Id.* at 9-10. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Applicant submits that *Wang*, alone, or in combination with the state of the art, does not teach all of the elements of the rejected claims.

Wang does not teach the pH range of 9.3 to 10. *Wang* teaches using a Pfu-Sso7d polymerase fusion with the standard reaction buffer for wild type Pfu polymerase, which contains 20 mM Tris-HCl (pH 8.8) as a buffering component. In addition to noting the standard pH 8.8 buffer, The Office also asserts that Wang teaches a buffer with a pH of 9.0. Office Action at page 5. The Office asserts "it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to use a pH of 9.3 and above as used by the

applicant or in the range of ph 9.0 as used by Wang, since these differences in pH would not be expected to greatly alter the conditions for amplification." *Id.* Applicant respectfully disagrees.

As an initial matter, the pH 9.0 buffer cited by the Office was not used for the Pfu-Sso7d polymerase fusion. Rather it was the buffer for a different polymerase, DyNAzyme EXT. *Wang* at p. 40, lines 12-14. As noted in *Wang*, "[t]he reaction buffer for Pfu-Sso7d was as described in Example 6-1 [i.e., pH 8.8]." *Id.*

In the previous response filed 17 December 2007, Applicant submitted a Declaration Under 37 C.F.R. § 1.132 by Michael Borns. According to the Office, the Declaration was insufficient to overcome the 103 rejection based on *Wang* because

> the declaration: (1) provides evidence only showing that a non-chimeric polymerase which is *PFU Turbo* loses activity above pH 8.8 (see Attachment B), whereas Wang teaches a chimeric polymerase which is a DNA polymerase fusion which functions at pH 9 (see Wang p. 40, line 14); (2) does not provide evidence that a sole chimeric polymerase which is a DNA polymerase fusion as claimed (that is, not a blend) functions at pH 9.3 to pH of 14 as claimed; and (3) thus does not provide evidence supporting an argument that it would have been a surprising discovery to one of ordinary skill in the art that a sole DNA polymerase fusion, as claimed, has enhanced PCR performance efficiency above pH 9.

Office Action at page 3. Applicant addresses each of these points in turn.

First, the Office dismisses the Declaration because it shows that a nonchimeric Pfu polymerase loses activity above pH 8.8, whereas *Wang* teaches a chimeric fusion polymerase that functions at pH 9.0.[1] *Id.* It appears that the Office takes issue with the fact that the data

[1] As noted above, the pH 9.0 buffer of *Wang* refers to a buffer for a different polymerase, DyNAzyme EXT.

discussed in the declaration relate to a non-chimeric Pfu polymerase whereas *Wang* discloses a chimeric Pfu fusion polymerase. However, in making this argument, the Office overlooks the statements in the Declaration that one of skill in the art would have expected high pH to affect a chimeric Pfu fusion polymerase and a non-chimeric Pfu polymerase in similar ways. Specifically, the Declaration states that "increasing the pH of the reaction buffer disclosed in Example 6.1 of Wang above a pH of 9 would significantly impair the conditions for amplification with Wang's Pfu-Sso7d fusion polymerase," just as it does for the wild type Pfu polymerase. Declaration, ¶ 16. Thus, the activity observed with the non-chimeric Pfu polymerase at pH greater than 9 is directly relevant to what one of skill in the art would have expected with respect to the activity of the chimeric Pfu fusion polymerase at pH conditions greater than 9. The Office does not acknowledge this fact.

Next, the Office argues that the Declaration does not provide evidence that a "sole chimeric polymerase," as opposed to a blend comprising "a chimeric polymerase," functions at pH 9.3 to 14. Office Action at page 3. As noted in the Declaration, however, this evidence is provided in the specification. Specifically, the Declaration states that "it was surprising when I discovered that increasing the pH of the reaction buffer above 9 enhances, rather than impairs, the PCR performance efficiency of the DNA polymerase fusions in U.S. Application No. 10/805,650, and blends comprising the same. *See* Figures 1-9 of the '650 application." Declaration, ¶ 18. Specifically, Figures 4-9 show that a chimeric fusion polymerase, which is

not part of a blend, efficiently amplifies various target sequence of different lengths at pH 10 and 11.8.[2] As noted in the specification:

- "The reactions which have 0.83U and 1.3U *Pfu*-Sso7d without any cloned *Pfu* DNA polymerase (#3 and #4 figure 4) generated dramatically higher yields than the blend reactions (#1 and #2 figure 4) . . . ." Specification at page 81, lines 10-14.
- "For all targets, the chimeric *Pfu*-Sso7d DNA polymerase in the high pH PCR reaction buffers displayed vastly superior performance at all unit amounts (0.25-1.3U per reaction)." Specification at page 82, lines 10-12.
- "By the use of a high pH reaction buffer with a processive chimeric Pfu DNA polymerase (in the presence of PEF/dUTPase), PCR extension times were substantially reduced for the amplification of genomic targets." Specification at page 82, line 13-15.

Thus, the specification provides evidence that both a Pfu-Sso7d fusion polymerase alone (i.e., not in a blend) and blends comprising the same show enhanced activity at high pH.

Finally, the Office asserts that the Declaration does not provide evidence to support an argument that it would have been surprising to one of ordinary skill in the art that "a sole DNA polymerase fusion, as claimed, has enhanced PCR performance efficiency as claimed." Office Action at page 3. This assertion is based on the faulty premise that the Declaration provides no evidence that a "sole chimeric DNA polymerase" functions at a pH greater than 9. As noted above, however, the Declaration refers to data in the specification (Figures 1-9) showing that

[2] Figures 1-4 similarly show that blends comprising a chimeric fusion polymerase efficiently amplify various target sequences at pH 9.5-12.

Pfu-Sso7d polymerase fusions, alone, or as a blend with additional polymerases, surprisingly, enhance—rather than impair—PCR performance at high pH.

Accordingly, as previously submitted, the Declaration, coupled with the specification, establish that one of ordinary skill in the art would expect that increasing the pH of the reaction buffer disclosed in Example 6.1 of Wang to a pH of 9.3 or higher would significantly impair the conditions for amplification with either the wild type Pfu DNA polymerase *or the Pfu-Sso7d fusion polymerase*. *See* Declaration, ¶ 16.

In support of its rejection, the Office asserts that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a pH of 9.3 and above as used by the applicant or in the range of ph 9.0 as used by Wang since these differences in pH would not be expected to greatly alter the conditions for amplification." Office Action at page 5. The Office further asserts that "a skilled artisan would expect a pH of 9.0 to have nearly identical properties in the amplification of nucleic acids." *Id.* at 6. As noted above, however, the Declaration directly refutes the Office's position. Specifically, the Declaration establishes that for Pfu polymerase and fusion proteins comprising the same, one of ordinary skill in the art would expect that increasing pH from 8.8, as used in Example 6-1 of *Wang* (or even 9) to 9.3 and above would significantly alter the conditions for amplification, transitioning from optimal amplification conditions around pH 8.8 to conditions (pH 9.3 and above) where little to no amplification would be expected because of small differences in pH. *See* Declaration, ¶ 16. Thus, the evidence of record establishes that at least with Pfu polymerase and fusion proteins comprising the same, one of ordinary skill in the art would have expected that small changes in

pH could lead to significantly different properties, including the loss of activity when the pH increases above 9. The Office provides no evidence or reasoning to call into question this evidence or to otherwise support its contentions that one of skill in the art would expect a Pfu polymerase or fusion protein comprising the same to have the same amplification properties at a pH of 9.0 or at 9.3 (claims 1-4, 7-11, 13, 15, 19, 25-30, and 41) or 9.5 (claims 42-46).

Without support, the Office also asserts that "[o]ne of ordinary skill in the art would have not expected that the activity of a DNA polymerase fusion would vanish at pH 9.3 when it was fully functional at pH 9.0." Office Action at page 5. As an initial matter, there is no evidence of record that the Pfu-Sso7d fusion proteins were "fully functional at pH 9.0." The Office's citation to a pH 9.0 buffer at page 40 of Wang refers to a buffer for DyNAzyme EXT not the Pfu-Sso7d fusion proteins. Even if the Pfu-Sso7d were fully functional at pH 9.0, however, the evidence of record establishes that small changes in pH have significant effects on the activity of Pfu polymerase and would have been expected to have similar effects on the activity of Pfu fusion proteins. As noted by the Office, the Declaration provides evidence that "a non-chimeric Pfu polymerase . . . loses activity above pH 8.8." Office Action at page 3; *see* Declaration, ¶¶ 11-14. Therefore, based on the evidence of record, one of ordinary skill in the art would not have expected that the reaction buffer in *Wang* would have the same properties if the pH were raised to 9.3 or higher. *See In re Peterson*, 315 F.3d at 1329. Rather the skilled artisan would have expected that raising the pH of the reaction buffer in *Wang* to 9.3 or higher would impair—not enhance—the efficiency of the disclosed Pfu-Sso7d fusion polymerases.

Finally, with respect to unexpected results, the Office asserts that "no evidence has been presented that the selection of pH 9.3 was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art of pH 9.0." Office Action at page 6. The Office further notes that "the features upon which applicant relies (i.e., "blends comprising DNA polymerases" show enhanced activity) are not recited in the rejected claim(s)." *Id.* at 7. As discussed above, however, the specification, including pages 78-82 and Figures 1-9 show that high pH surprisingly enhances—rather than impairs—the amplification properties (including decreased extension times) of *both* a Pfu-Sso7d fusion polymerase and blends comprising the same. Therefore, it is not just the blends that show enhanced activity at high pH—it is also the Pfu-Sso7d fusion polymerase alone (i.e., not in a blend). Thus, contrary to the assertions by the Office, Applicant has demonstrated unexpected results for the claimed Pfu-Sso7d fusion polymerases, as well as blends comprising the same.

Accordingly, for the reasons of record and the reasons discussed above, Applicant submits that *Wang*, alone, or in combination with the state of the art, fails to teach or suggest all elements of claims 1-4, 7-11, 13, 15, 19, 25-30, and 41-46 and, thus, does not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 41-46 as unpatentable over *Wang*.

B. *Wang* in Combination with *Sanger* Does Not Render Claims 5 and 6 Obvious

The Office maintains the rejection of claims 5 and 6 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang* in combination with *Sanger*. Office Action at page 7. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2142. Applicant submits that the combined teachings of the cited references do not teach all of the elements of the rejected claims. For the reasons discussed above, *Wang* fails to teach or suggest a pH from 9.3 to 14 (claims 1-4, 7-11, 13, 15, 19, 25-30, and 41) or from 9.5 to 12 (claims 42-46). *Sanger* also fails to teach or suggest this element of the claims and thus fails to remedy the deficiencies of *Wang*.

Accordingly, Applicant submits that the combined teachings of *Wang* and *Sanger* fail to teach or suggest all elements of claims 5 and 6 and, thus, do not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 5 and 6 as unpatentable over the combination of these references.

V. Conclusion

In view of the foregoing amendment and remarks, Applicant submits that this application is in condition for allowance. Applicant therefore requests entry of this amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
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